

Sandhoff Disease—A Case Report of 3 Siblings and a Review of Potential Therapies

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Abstract

Introduction: Sandhoff disease is a G_{M2} gangliosidosis that may present within the first 6 months of life with developmental regression. This is the first report of a pedigree from Southeast Asia. **Clinical Picture:** All the affected siblings presented in the first year of life with developmental regression, spasticity, seizures and loss of vision. The diagnosis was confirmed by an enzymatic deficiency in both β -hexosaminidase A and B. **Conclusion:** As the disorder is autosomal recessive, and no curative therapy is currently available, genetic counselling is necessary to prevent the burden of this devastating disease. We review the potential strategies of treatment for Sandhoff disease.

Ann Acad Med Singapore 2000; 29:514-7

Key words: Autosomal recessive, β -hexosaminidase, Bone marrow transplant, Developmental regression, G_{M2} gangliosidosis

Introduction

Sandhoff disease is a rare inborn error of metabolism characterised by the absence of both β -hexosaminidase A and B, resulting in an accumulation of G_{M2} gangliosides, particularly in the neuronal cells.¹ The infantile form, similar to Tay Sach's disease, may present in the first year of life with an exaggerated response to loud noises, delay or loss of developmental milestones and loss of visual attentiveness. Described here are 3 siblings who presented with the classical picture of regression of milestones, progressive spasticity, blindness, seizures and exaggerated startle response.

Case Report

The elder male sibling, LYX, was born well at term, with good Apgar scores and birth weight of 3.1 kg. He was the first child of non-consanguineous Chinese parents. He had normal milestones initially, and by 8 months of age, he was able to reach out and grasp objects, sit without support and say "papa" and "mama". Subsequently, he gradually lost these milestones, and by 12 to 13 months, he was unable to say any words and was unable to sit without support.

He was referred for "delayed" development at 14 months of age. At that time, there was increased startle response to

loud sounds. He also had short and frequent daily tonic seizures as well as dystonic posturing.

On examination at the time of presentation, he had a weight of 7.9 kg (3rd percentile), recumbent length of 75.7 cm (25th percentile) and occipito-frontal circumference of 46.0 cm (25th percentile). There were no dysmorphic features. His hands were fisted, and his feet were in an equinus position (Fig. 1, right). There was increased tone in all 4 limbs with generalised hyper-reflexia and bilateral extensor plantar responses. Head lag was present, and he had no social smile or spontaneous vocalisation. He was able to visually fixate and follow 180°. Prominent startle response was present. There was no organomegaly.

An electroencephalogram demonstrated poor background organisation with moderate diffuse slowing in waking, and the presence of multifocal epileptiform discharges over both frontal regions in sleep. A computed tomography (CT) scan of the head was normal. Serum ammonia and lactate levels were normal. Serum and urine aminograms were unremarkable. He was started on sodium valproate with some reduction in seizure frequency. The dystonic posturing was unresponsive to haloperidol.

Over the next 6 months, he continued to regress and had progressively increasing spasticity. There was progressive

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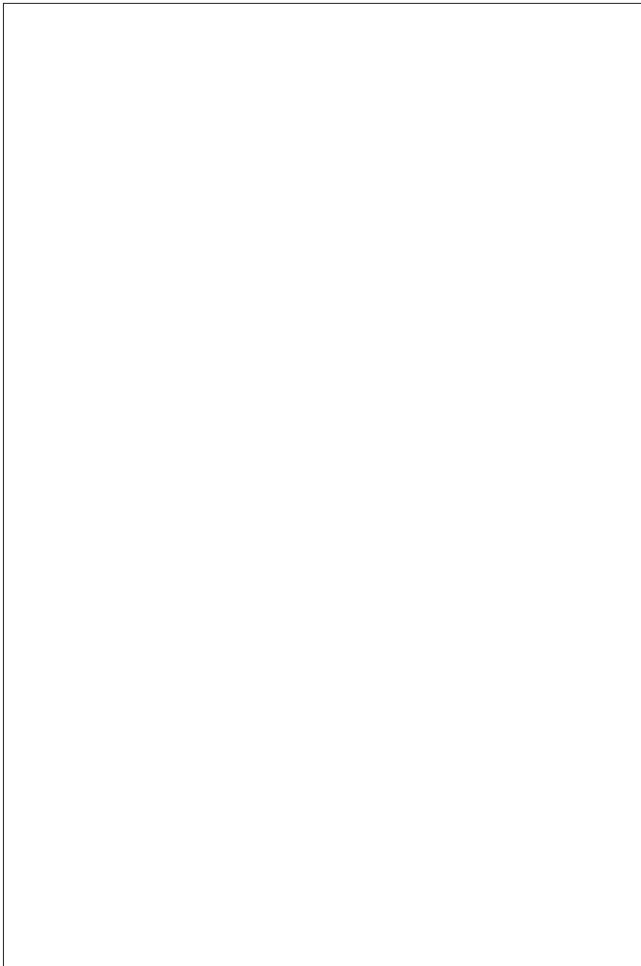


Fig. 1. Spasticity in the 2 elder siblings diagnosed with Sandhoff disease. Second affected female sibling, LWH, is on the left and eldest male sibling, LYX, is on the right.

extensor posturing, increased tone and contractures of the tendoachilles bilaterally. He lost the ability to visually fixate. Fundoscopy revealed cherry red spots in both eyes. A magnetic resonance imaging (MRI) of the brain showed fairly symmetrical, abnormal, increased signal intensity involving the caudate and lentiform nuclei, optic radiations, corona radiata and periventricular white matter, especially in the posterior parietal and occipital regions. Nerve conduction showed delayed motor conduction velocities. Sensory conduction study could not be performed because of excessive movement artefacts. Sural nerve biopsy was normal. Assay of lysosomal enzymes (Table I) of skin

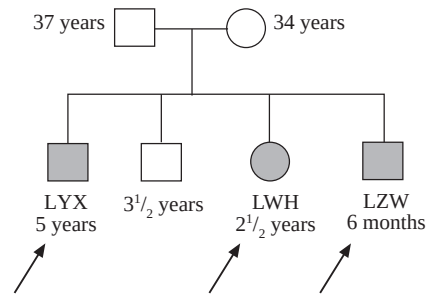


Fig. 2. Family tree of affected probands.

fibroblast culture showed extremely low total β -hexosaminidase activity (136 nmol/mg protein/h compared with control of 3218 nmol/mg protein/h), compatible with Sandhoff disease.

Genetic counselling was given to the parents. In this particular family, however, the parents' informed choice was to continue to have children despite repeated genetic counselling and recommendation for antenatal diagnosis. The second child was unaffected, but the third and fourth children were found to have low hexosaminidase levels (Fig. 2). There was significant denial on the parents' part that the disease was an inherited disorder, and it was only after the diagnosis of the third affected child that they were convinced.

The second affected sibling, LWH, had normal milestones for the first 8 months of life. Regression of milestones began after 6 months and by 12 months, she was only able to tripod sit and was unable to say any words.

On examination, she weighed 7.9 kg (3rd to 10th percentile), her recumbent length was 76.0 cm (10th to 25th percentile) and her head circumference was 45.0 cm (3rd to 10th percentile). At presentation, her neurological examination was unremarkable, except for mild hyper-reflexia and an exaggerated startle response. Bilateral cherry red spots were also present on fundoscopy. Her mother refused initial investigations except for an MRI scan of the brain that was performed at 3 months, which demonstrated poor myelination of the corticospinal tracts, internal capsule, corona radiata and other cerebral hemisphere white matter tracts. When the child was 17 months of age and had further progression of symptoms with increased spasticity (Fig. 1,

TABLE I: LYSOSOMAL ENZYME ASSAY RESULTS

Patient	β -hexosaminidase (nmol/mg protein/h)	Controls (nmol/mg protein/h)	β -hexosaminidase A (nmol/mg protein/h)	Controls (nmol/mg protein/h)
LYX	136	3218	Not done	Not done
LWH	74.2	2300	Absent	1200
LZW	84.2	1618	84.2	691

left), poor visual fixation and generalised tonic clonic seizures, a lysosomal enzyme assay (Table I) confirmed Sandhoff disease as β -hexosaminidase was low (74.2 nmol/mg protein/h with normal control 2300 nmol/mg protein/h) and β -hexosaminidase A was absent (normal value of 1200 nmol/mg protein/h). Bone marrow transplant was considered for this child, as she had a full HLA match as her normal elder brother. However, since there was already significant neurological impairment, the transplant was not performed.

Both the older affected siblings have continued to regress and deteriorate. Both became severely spastic and bed-bound, and were completely dependent in all aspects of daily living. LYX died at 5 years of age of pneumonia.

The last sibling, LZW, was found to have mild increased tone in the lower limbs on examination at 5 months of age and the presence of cherry red spots on fundoscopy. At presentation, he had normal growth parameters, with weight at 7.23 kg (50th centile), height of 63.5 cm (50th centile), and occipitofrontal circumference of 42.0 cm (50th centile). He was able to roll over, but was unable to bear weight. The lysosomal hexosaminidase levels (Table I) were low (β -hexosaminidase levels of 84.2 nmol/mg protein/h with control of 1618 nmol/mg protein/h and β -hexosaminidase A levels of 84.2 nmol/mg protein/h with controls of 691 nmol/mg protein/h), confirming the diagnosis of Sandhoff disease.

Discussion

Sandhoff disease, like Tay-Sach's disease, is a G_{M2} gangliosidosis, and is an autosomal recessive disease characterised by the accumulation of G_{M2} gangliosides, resulting in damage to neuronal cells. The enzymatic defect is a deficiency in hexosaminidase A and B, whereas in Tay-Sach's disease, there is a deficiency in hexosaminidase A² only. The hexosaminidase enzyme consists of two subunits; hexosaminidase A that is made up of 1 α and 1 β subunit, whereas hexosaminidase B is made up of 2 β subunits. There is a defect in or absence of the β subunit in Sandhoff disease and an absence of the α subunit in Tay-Sach's disease. At least 14 mutations have been identified in the *HEXB* gene that encodes the β subunit of hexosaminidase, the most common mutation being a deletion in the promoter, and part of intron 5 of the *HEXB* gene.³

Sandhoff disease was first described as a variant of Tay-Sach's disease by Sandhoff et al⁴ in 1968, in a child with visceromegaly. In the infantile form, the onset is within the first year of life, and may present with an increased startle reaction, early blindness, progressive mental and developmental regression, doll-like face and cherry red spots. After the first year of life, there is progressive

psychomotor regression with worsening spasticity, dysfunctional swallowing and seizures. Macrocephaly may be present in the second year of life because of the swelling of the cerebral white matter. Death may occur from 2 to 5 years of age, usually due to aspiration pneumonia.

This is the first report from Southeast Asia of Sandhoff disease confirmed by enzymatic studies. The 3 siblings had similar presentations in that they had relatively normal milestones in the first 6 months of life, but demonstrated progressive psychomotor retardation in the later part of infancy. In addition, they had a prominent startle response, progressive spasticity, worsening vision and cherry red spots. The cherry red spot is a dull red spot that is the centre of the macula, surrounded by a yellowish-white halo that results from the loss of transparency of the multilayered ganglion cell ring due to oedema and accumulation of lipids. None had hepatosplenomegaly, however, which may be found in some patients with Sandhoff disease. Seizures were a relatively early feature in the course of their disease, and have proven to be more difficult to control with time, due to increasing neurological degeneration.

The findings of the MRI of the brain of the elder sibling at 20 months of age were consistent with what has been reported previously, as he had increased signal intensity affecting the optic radiation and basal ganglia. There were also white matter changes in the parietal and occipital periventricular regions that may have been secondary to demyelination. It has been reported that thalamic hyperdensity from calcifications may be an early and constant sign of gangliosidosis,⁵ and this may be seen more clearly on CT scan of the brain. The younger sibling had an MRI scan of the brain very early on at 3 months of age at the pre-symptomatic stage, and the child already had features of abnormal myelination of the white matter tracts. These MRI findings are typical of the evolution of degenerative changes that may be seen in Sandhoff disease.⁶

Both siblings were treated symptomatically with anticonvulsants for seizure control, physiotherapy for spasticity, and nasogastric feeding for poor swallowing. They were bed-bound and completely dependent in all aspects of daily living. Presently, there is no specific therapy for patients with Sandhoff disease. However, various experimental strategies have been tried out on Sandhoff disease animal models. These strategies may focus on either substrate deprivation or enzyme augmentation.

Substrate deprivation has been tried in the mouse model with *N*-butyldeoxynojirimycin, which is a potent inhibitor of glycosphingolipid synthesis. Jeyakumar et al⁷ recently reported delayed symptom onset and increased life expectancy in Sandhoff disease mice treated with *N*-

butyldeoxynojirimycin. The advantage of *N*-butyldeoxynojirimycin is that it can cross the blood-brain barrier and thus, achieve significant decreases in ganglioside storage in the brain.

Enzyme augmentation by other means such as bone marrow transplant is dependent on the stage of the disease and the effects the disease have on various organs. "Visceral" manifestations respond well, but the nervous system abnormalities respond variably to transplant.⁸ Norflus et al⁹ were able to demonstrate an increase in the β -hexosaminidase activity and enzyme-positive cells in the brain and spinal cord of the mice after bone marrow transplant. This is likely to be due to enzyme introduction into the central nervous system by donor macrophages and microglia.¹⁰

Gene therapy is another strategy³ that may offer a cure but has significant practical problems. The appropriate vector has not yet been found as the vectors that infect neurones do not show long-term expression of the transgene at the site of the infection, and the vectors that do have stable expression of the transgene do not have affinity for neurones.¹¹

Although many promising strategies do exist for the potential treatment of Sandhoff disease, these may not do much more than delay the progress of disease, and prolong survival without decreasing morbidity or mortality. Bone marrow transplant was considered for the second affected sibling as she had full HLA match with the normal brother, but was not carried out because of her extremely poor neurological status at that time. Although early diagnosis was made for the last sibling LZW, no matched sibling bone marrow transplant was available. At present, the best option available is prevention of the disease itself. Genetic counselling therefore takes centre stage in the management of any child with Sandhoff disease. The concept of an inherited metabolic disorder is often alien in the local cultural context. For this family to accept that the disease was transmissible was extremely difficult and thus, they did not avail themselves to the resources available for prenatal diagnosis and refused to consider other avenues such as adoption or artificial insemination.

Conclusion

Sandhoff disease is a rare metabolic disorder that has devastating effects on the patients and family members. This case report illustrates that while there are many exciting modalities of treatment that are being explored, these have not gone beyond trials in animal models. As such, the mainstay of treatment is genetic counselling and prevention of the disease either by exploring alternative reproductive options or prenatal diagnosis. Failure of genetic counselling in this case may have been due to parental denial and the inability to grasp the concept of a transmissible genetic disorder.

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